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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 09/593,316 | 06/13/2000 | John Clark | 730/002 | 5627 |

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| EXAMINER |
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LI, QIAN J

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| ART UNIT | PAPER NUMBER |
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1632

DATE MAILED: 05/06/2003

21

Please find below and/or attached an Office communication concerning this application or proceeding.

Advisory Action

Application No.

09/593,316

Applicant(s)

CLARK ET AL.

Examiner

Q. Janice Li

Art Unit

1632

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 04 April 2003 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE. Therefore, further action by the applicant is required to avoid abandonment of this application. A proper reply to a final rejection under 37 CFR 1.113 may only be either: (1) a timely filed amendment which places the application in condition for allowance; (2) a timely filed Notice of Appeal (with appeal fee); or (3) a timely filed Request for Continued Examination (RCE) in compliance with 37 CFR 1.114.

PERIOD FOR REPLY [check either a) or b)]

- a) ☐ The period for reply expires _____ months from the mailing date of the final rejection.
- b) ☒ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection. ONLY CHECK THIS BOX WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

1. ☐ A Notice of Appeal was filed on _____. Appellant's Brief must be filed within the period set forth in 37 CFR 1.192(a), or any extension thereof (37 CFR 1.191(d)), to avoid dismissal of the appeal.
2. ☐ The proposed amendment(s) will not be entered because:
- (a) ☐ they raise new issues that would require further consideration and/or search (see NOTE below);
 - (b) ☐ they raise the issue of new matter (see Note below);
 - (c) ☐ they are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
 - (d) ☐ they present additional claims without canceling a corresponding number of finally rejected claims.

NOTE: _____.

3. ☐ Applicant's reply has overcome the following rejection(s): _____.
4. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
5. ☒ The a) ☐ affidavit, b) ☐ exhibit, or c) ☒ request for reconsideration has been considered but does NOT place the application in condition for allowance because: See Continuation Sheet.
6. ☐ The affidavit or exhibit will NOT be considered because it is not directed SOLELY to issues which were newly raised by the Examiner in the final rejection.
7. ☐ For purposes of Appeal, the proposed amendment(s) a) ☐ will not be entered or b) ☐ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.

The status of the claim(s) is (or will be) as follows:

Claim(s) allowed: _____.

Claim(s) objected to: _____.

Claim(s) rejected: _____.

Claim(s) withdrawn from consideration: _____.

8. ☐ The proposed drawing correction filed on _____ is a) ☐ approved or b) ☐ disapproved by the Examiner.
9. ☒ Note the attached Information Disclosure Statement(s) (PTO-1449) Paper No(s). 16, 19.
10. ☐ Other: _____

ANNE M. WEHBE' PH.D
PRIMARY EXAMINER

Continuation of 5. does NOT place the application in condition for allowance because: Applicants submitted a newly published paper by Phelps et al and argue because the article describes pigs that are homozygously inactivated for the a1,3GT gene, it confirms that the specification of the present application is enabled for the making of a homozygous a1,3GT knockout sheep. In response, the Phelps reference does not provide enablement for making of a homozygous a1,3GT knockout sheep for reasons that follow.

As discussed in the personal interview conducted on 3/25/03 with the Examiner and the Supervisory Examiner and indicated in the previous actions, because the genetic make-up and variations among different species of large animals, it is unpredictable from the results of a pig to the phenotype of a sheep, particularly in light of the comparison between the Denning reference (the attempt for making a heterozygous knock-out sheep) and the Dai and Lai references (produced piglets knock-out of one allele of the pig a1,3GT gene). Applicants concluded drawn from the observation of Phelps et al, "homozygous knockout cells can be made by targeting the other allele in the donor cells using a knockout vector", and selecting cells deficient in the particular surface antigen. However, the Phelps reference teaches the contrary, "ALTHOUGH OUR INTENT WAS TO KNOCK OUT THE SECOND ALLELE OF THE a1,3GT GENE BY HOMOLOGOUS RECOMBINATION, THIS DID NOT OCCUR" (lines 1-4, right column, page 413).

Applicants then state that knockout cells can be used as donor cells for nuclear transfer to produce homozygous knockouts. However, the specification fails to teach or produce a homozygous knockout cell in the way Phelps et al did, and the specification fails to generate a heterozygous knockout sheep that could be used for breeding, thus, the homozygous knockout sheep could not have been produced. Therefore, the basis for the assumption does not exist.

With regard to the Denning reference, applicants argue that the reference does not support that gene targeting in sheep is an uncertain process but illustrated the viability of the claimed invention. Particularly, sheep cells can be correctly targeted for inactivation of the a1,3GT gene, targeted cells can be used for nuclear transfer, and knockout of the a1,3GT gene does not decrease viability of the embryo. The arguments are not persuasive for reasons of record and following.

The claims are NOT drawn to a heterozygous embryo, instead, they drawn to homozygous knockout cells, tissue, and sheep. Denning reference only successfully made heterozygous a1,3GT gene knockout cells, and heterozygous a1,3GT knockout embryos, no live birth was achieved for a1,3GT knockout lamb. Additionally, Denning reference teaches the difficulties of cell targeting, "A SUBSTANTIAL NUMBER OF COLONIES WITH ONLY TARGETED CELLS SENESCED BEFORE THEY COULD BE PREPARED FOR NUCLEAR TRANSFER. THE HIGH ATTRITION RATE OF TARGETED CLONAL POPULATIONS SUITABLE FOR NUCLEAR TRANSFER REPRESENTS ONE OF THE MAJOR HURDLES OF GENE TARGETING IN PRIMARY SOMATIC CELLS" (left column, page 560).

With regard to rejections under 35 USC § 112, 1st paragraph, Applicants first argue that some of the pending claims do not require that a1,3GT knockout sheep be made, particularly claims 4, 5, and 33-37.

In response, these claims are drawn to heterozygous as well as homozygous inactivation of an a1,3GT gene, the later requires knockout of both alleles. The specification teaches, "such cells [homozygous knockout] and tissues can be obtained from a whole animal such as a sheep that is homozygous for inactivation of an a1,3GT gene" (Specification, page 7, lines 14-15). However, as indicated supra, this approach is not enabled according to the teaching of the specification and the Denning reference. The specification then teaches, "If the birthed animal is heterozygous for a1,3GT inactivation, homozygous inactivation can be achieved by selective breeding, or by a second round of gene targeting to inactivate the second allele" (Specification, page 7, lines 19-20). Because no live birth of lamb heterozygous for a1,3GT inactivation, the selective breeding could not be done. With regard to the second round of gene targeting to inactivate the second allele, the specification, as indicated by applicants in pages 40-41, teaches the outline of an art known procedure which so far had little success if any. The state of the art teaches that double knockout by gene targeting and homozygous recombination is extremely difficult to achieve for reasons to be determined. In fact, the very publication by Phelps et al in the newly submitted IDS evidenced such difficulty. Phelps et al teach, "THE FACT THAT ONE NORMAL-SIZED ALLELE WAS OBSERVED (INSTEAD OF TWO SHORTER KNOCKOUT ALLELES) INDICATED THAT KNOCKOUT OF THE SECOND a1,3GT ALLELE WAS DUE TO MECHANISMS OTHER THAN TARGETED HOMOLOGOUS RECOMBINATION-MEDIATED DISRUPTION, PROMOTER DYSFUNCTION, OR MRNA MISPLICING AND INSTABILITY" (mid- and right column, page 412). They go on to teach a toxin A selection method for a1,3GT-negative cells and its importance in achieving the double knockout of a1,3GT gene. "ALTHOUGH OUR INTENT WAS TO KNOCK OUT THE SECOND ALLELE OF THE a1,3GT GENE BY HOMOLOGOUS RECOMBINATION, THIS DID NOT OCCUR. INSTEAD, BECAUSE WE USED THIS POWERFUL SELECTION METHOD, WHICH ALLOWS US TO ISOLATE ANY EVENT THAT RESULTS IN LOSS OF a1,3GT ACTIVITY, WE DISCOVERED A MUTATION IN THE SECOND ALLELE OF THE a1,3GT GENE. HAD WE USED STANDARD SELECTION METHODS WITH PUROMYCIN OR HYGROMYCIN, WE WOULD NOT HAVE FOUND THE MUTATION" (right column, page 413). The specification fails to teach why double knockout in a cell is so difficult to achieve, and how to overcome the art known hurdles, accordingly, fails to provide an enabling disclosure. The specification fails to teach the mutation and selection methods taught by Phelps et al, thus, a later advance in cloning technology does not enable the specification at the time the application was filed. The statute requires, "THE SPECIFICATION SHALL CONTAIN A WRITTEN DESCRIPTION OF THE INVENTION, AND OF THE MANNER AND PROCESS OF MAKING AND USING IT, IN SUCH FULL, CLEAR, CONCISE, AND EXACT TERMS AS TO ENABLE ANY PERSON SKILLED IN THE ART TO WHICH IT PERTAINS, OR WITH WHICH IT IS MOST NEARLY CONNECTED, TO MAKE AND USE THE SAME AND SHALL SET FORTH THE BEST MODE CONTEMPLATED BY THE INVENTOR OF CARRYING OUT HIS INVENTION". The court states, "IF INDIVIDUALS OF SKILL IN THE ART STATE THAT A PARTICULAR INVENTION IS NOT POSSIBLE YEARS AFTER THE FILING DATE, THAT WOULD BE EVIDENCE THAT THE DISCLOSED INVENTION WAS NOT POSSIBLE AT THE TIME OF FILING AND SHOULD BE CONSIDERED. IN IN RE WRIGHT, 999 F.2D 1557, 1562, 27 USPQ2D 1510, 1513-14 (FED. CIR. 1993)

With respect to arguments that there are issued patents claiming similar subject matter, the court (In re Giolito and Hofmann, 188 USPQ 645 (CCPA 1976)) states "IT IS IMMATERIAL WHETHER SIMILAR CLAIMS HAVE BEEN ALLOWED TO OTHERS. SEE IN RE MARGAROLI, 50 CCPA 1400, 318 F.2D 348, 138 USPQ 158 (163); IN RE WRIGHT, 45 CCPA 1005, 256 F.2D 583, 118 USPQ 287 (158); IN RE LAUNDER, 41 CCPA 887, 212 F.2D 603, 101 USPQ 391 (1954)." Each application is examined on its own merits and cannot be compared to other application.

With regards to rejections under 35 USC § 112, 1st paragraph, Applicants then argue that the Office has not established that a1,3GT knockout sheep cannot be made.

The arguments are reiterations of previous arguments, which have been addressed in the previous Office action paper Nos. 7, 12, 17, and above, will not be reiterated here. The only addition should be the following statement in the MPEP.

"WHEN CONSIDERING THE FACTORS RELATING TO A DETERMINATION OF NON-ENABLEMENT, IF ALL THE OTHER FACTORS POINT TOWARD ENABLEMENT, THEN THE ABSENCE OF WORKING EXAMPLES WILL NOT BY ITSELF RENDER THE INVENTION NON-ENABLED." "LACK OF A WORKING EXAMPLE, HOWEVER, IS A FACTOR TO BE CONSIDERED, ESPECIALLY IN A CASE INVOLVING AN UNPREDICTABLE AND UNDEVELOPED ART." (MPEP 2164.02, 03)

Applicants filed a Request to Vacate Finality of Office action on the ground that the Office action does not provide an explanation as to why the cells covered by claims 4, 5, and 33-37 are not described and enabled by the specification as filed.

The request has been carefully considered but not granted for reasons of record advanced in the previous Office action paper Nos. 7, 12, 17, and the immediate preceding section.